CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201201649

Stereocontrolled Total Synthesis of (+)-*trans*-Dihydronarciclasine

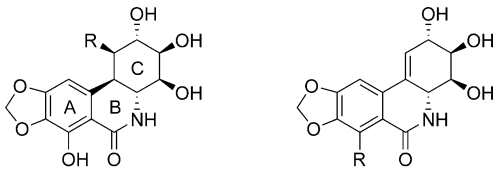
Soonho Hwang, Deukjoon Kim, and Sanghee Kim*[a]

Abstract: A highly stereoselective and efficient total synthesis of *trans*-dihydronarciclasine from a readily available chiral starting material was developed. The synthesis defines two of the five stereogenic centers of the natural product by an amino acid ester–enolate Claisen rearrangement. The other three stereogenic centers are created in a highly stereocontrolled fashion via a six-ring vinylogous ester intermediate, which is generated from the γ,δ-unsaturated ester functional group of the Claisen rearrangement product in an efficient three-step sequence. This concise total synthesis exemplifies the use of a highly regioselective Friedel–Crafts-type cyclization to form the B ring via an isocyanate intermediate derived from an *N*-Boc group, which is superior to the conventional method using an imino triflate intermediate. This same *N*-Boc group is employed to give high selectivity in the Claisen rearrangement earlier in the sequence.

Keywords: acid-mediated cyclization · antitumor agents · Ireland–Claisen rearrangement · natural products · total synthesis

Introduction

Based on their potent and selective anticancer activity, as well as their unique structural features, *Amaryllidaceae* isocarbostyril alkaloids have been an attractive synthetic target for the last two decades.[1,2] Some representative members of this class of natural products are *trans*-dihydronarciclasine (**1**), pancratistatin (**2**), lycoricidine (**3**), and narciclasine (**4**, Figure 1). These natural isocarbostyrils exhibit potent cytotoxicity in the NCI 60 human tumor cell line panel with GI_{50} values in the nanomolar range.[3] Although *trans*-dihydronarciclasine has far greater anticancer activity than the intensively investigated pancratistatin (**2**) and other congeners,[3b] less effort has been devoted to biological and synthetic studies on *trans*-dihydronarciclasine until recently.[4]



trans-dihydronarciclasine (**1**, R = H)
pancratistatin (**2**, R = OH)

lycoricidine (**3**, R = H)
narciclasine (**4**, R = OH)

Figure 1. Chemical structures of compounds **1**–**4**.

The isolation of (+)-**1** from the Chinese medical plant *Zephyranthes candida* was reported in 1990.[5] Interestingly, long before its isolation from natural sources, it was produced synthetically through hydrogenation of narciclasine (**4**) with low diastereoselectivity.[6] The first total synthesis of the racemate was reported by Cho in 2007,[4a] which involved a Diels–Alder cycloaddition of 3,5-dibromo-2-pyrone for the preparation of the functionalized C ring. The first enantioselective synthesis by Studer was published in 2008,[4b] in which the required absolute stereochemistry of the C ring was introduced by a Cu-catalyzed enantioselective nitroso Diels–Alder reaction. Both syntheses employed Banwell's modified Bischler–Napieralski reaction at a late stage of the sequence for closure of the B ring.

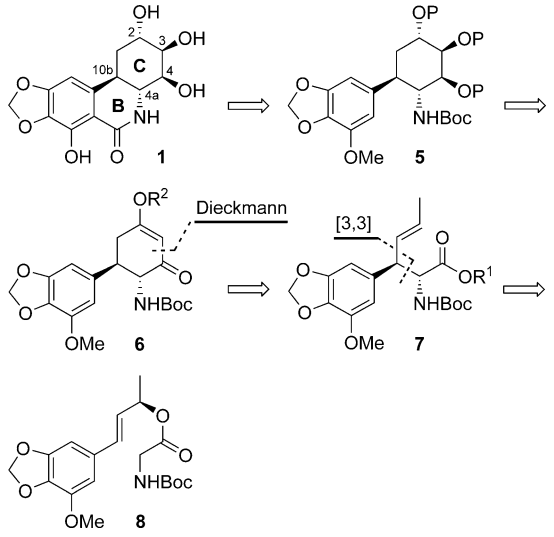
Herein, we wish to describe a short and highly stereocontrolled total synthesis of (+)-**1** by a strategy that is unique compared to other previous syntheses of *Amaryllidaceae* isocarbostyril alkaloids. Our route is characterized by the use of an *N*-Boc group, first to steer the stereochemical course of a Claisen rearrangement and then, to generate an isocyanate intermediate for a highly regioselective Friedel–Crafts-type B-ring cyclization. This approach is superior to using the conventional Bischler–Napieralski-type B-ring cyclization, especially in the sense of regioselectivity.

Results and Discussion

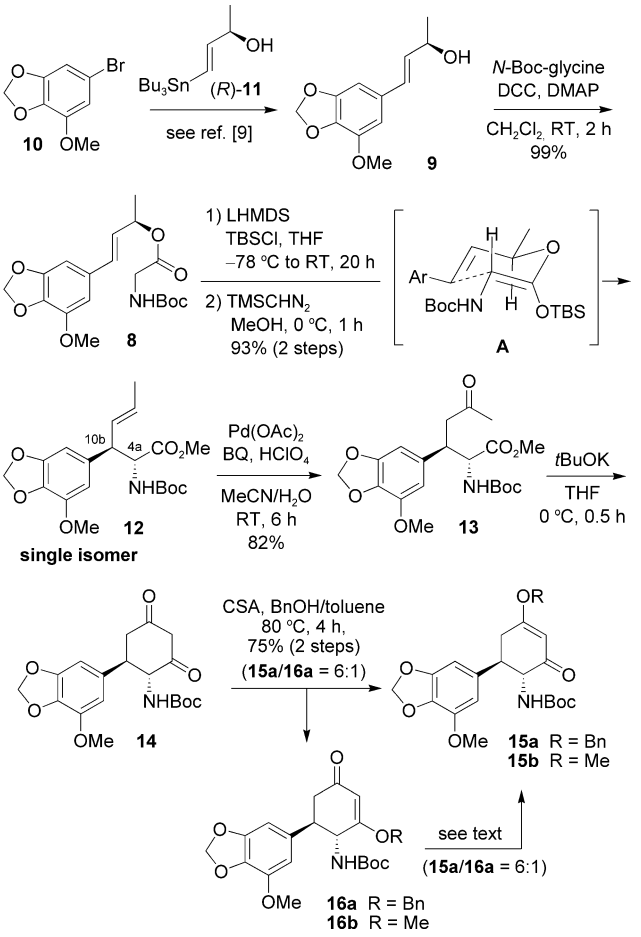
Retrosynthetic analysis: As shown in Scheme 1, we planned to construct the B ring of **1** at a late stage of the synthesis, similar to many other *Amaryllidaceae* isocarbostyril synthetic approaches. We envisioned that the construction of the B ring could be achieved by utilizing the *N*-Boc carbamate group in compound **5**, in which this group is also essential for attaining high stereocontrol in the subsequent transfor-

[a] S. Hwang, Prof. Dr. D. Kim, Prof. Dr. S. Kim
College of Pharmacy, Seoul National University
San 56-1, Shilim, Kwanak
Seoul 151-742 (Korea)
Fax: (+82) 2-888-0649
E-mail: pennkim@snu.ac.kr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201201649.



Scheme 1. Retrosynthetic analysis of *trans*-dihydronarciclasine (**1**).



Scheme 2. Synthesis of intermediate **15**. DCC = *N,N*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, LHMDS = litium hexamethyl disilazide, TBSCl = *tert*-butyldimethylsilylchloride, BQ = benzoquinone, CSA = camphorsulfonic acid.

mations (see below). Our strategy was premised on the selective transformation of the β-keto enol ether function of **6** to the three contiguous hydroxyl groups of the C ring of **5**. We expected that cyclic vinylogous ester **6** could be obtained regioselectively from the γ,δ-unsaturated ester **7** by regioselective Wacker oxidation, Dieckmann condensation, and regioselective vinylogous ester formation. We further envisioned that an ester–enolate Claisen rearrangement of the Boc-protected amino acid allylic ester **8** would provide the γ,δ-unsaturated α-amino ester **7**.[7] In this transformation, the required stereochemistry of the two contiguous stereocenters at C-4a and C-10b could be installed with chirality transfer from a preformed chiral center in substrate **8** via a chair-like transition state. The Boc group was chosen as the amino protecting group, because the stereoselectivity of ester–enolate Claisen rearrangements of Boc-protected amino esters is generally superior to that of other carbamate-protected amino esters.[8] In addition, the bulkiness of the Boc group was expected to promote high selectivity through steric interactions or conformational reinforcement, especially in the introduction of the three contiguous hydroxyl-group stereocenters.

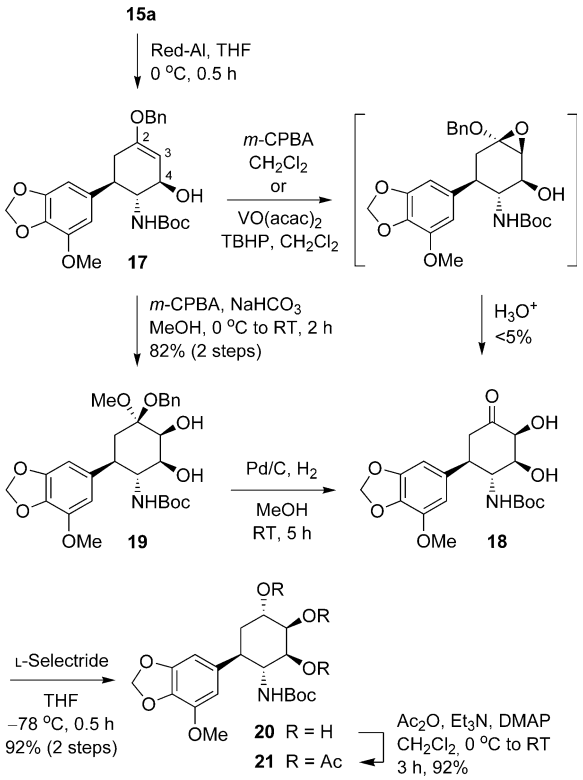
Synthesis of the A–C ring systems: As illustrated in Scheme 2, the synthesis was initiated by preparing Claisen substrate **8** from the enantiomerically enriched allylic alcohol **9**. The synthesis of **9** from the aryl bromide **10** and chiral building block (*R*)-**11** (>99% *ee*) was previously reported by us in the total synthesis of **2**.[9] Allylic alcohol **9** was then coupled with *N*-Boc-glycine to provide the chiral allylic amino acid ester **8**. After some experimentation, we identified conditions that led to the formation of the desired rearranged product **12** in excellent stereoselectivity and yield. Deprotonation of **8** at −78 °C with LHMDS in THF in the presence of TBSCl resulted in the formation of the (*Z*)-silyl ketene acetal intermediate, which underwent Claisen rearrangement upon gradual warming to room temperature to afford **12** (93%) after treatment with TMS-diazomethane.[10] A single diastereomer was observed by NMR and HPLC analysis. The absolute configurations of the two new stereocenters were assumed to be 4a*R* and 10b*R* by invoking chair transition state **A** for the rearrangement, and these configurations were ultimately confirmed by conversion to the final natural product.

Next, efforts were directed toward forming the C ring by a two-step process that began with regioselective oxidation of the internal olefin to afford methyl ketone **13**. The resulting intermediate could then undergo Dieckmann condensation to give cyclic β-diketone **14**. In the event, highly regioselective (8:1) Wacker oxidation of olefin **12** could be achieved in 82% yield with $Pd(OAc)_2$ and benzoquinone (BQ).[11] Condensation of **13** by using *t*BuOK in THF provided the desired β-diketone **14**, which was used directly in the next step without further purification.[12]

C-Ring functionalization: Our approach to functionalize the C3 position was to convert the cyclic β-diketone moiety of **14** to the corresponding vinylogous ester by enol etherifica-

tion. The regiochemical outcomes of etherification of asymmetric cyclic β-diketones are often difficult to predict, and mixtures of the two possible products are frequently produced.[13] However, we envisioned that enol etherification of **14** would be regioselective under thermodynamic conditions, since vinylogous ester **15** was expected to be thermodynamically more stable than its regioisomer **16**, primarily owing to the lower steric strain. Some support was obtained from our computational modeling studies, which predicted that **15b** would be more stable than **16b** by 1.36 kcal mol^{-1}.[14] As expected, treatment of crude **14** with benzyl alcohol and a catalytic amount of CSA in toluene at 80 °C led to the selective formation of vinylogous benzyl ester **15a** (64% yield from **13**), along with a minor amount of its regioisomer **16a** (6:1). **16a** could be recycled by chromatographic separation, followed by resubjection to the above etherification conditions to isomerize it back to the 6:1 mixture in favor of **15a**.[15]

Next, our study focused on the selective conversion of the β-keto enol ether function of **15a** into the triol **20** (Scheme 3). First, the carbonyl group of **15a** was stereoselectively reduced with Red-Al to give exclusively the required 4β-hydroxy group. Since allylic alcohol **17** was unstable,[13c,16] it was immediately used in the next step without chromatographic purification. Dihydroxylation of the enol ether **17** under the Upjohn dihydroxylation conditions (OsO_4, NMO = *N*-methylmorpholine *N*-oxide)[17] afforded



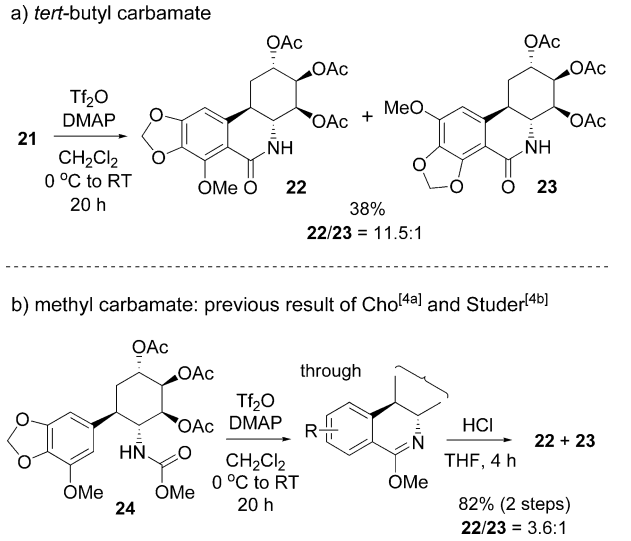
Scheme 3. Introduction of the stereocenters in the C ring. Red-Al = sodium bis(2-methoxyethoxy)aluminum dihydride, *m*-CPBA = *meta*-chloroperbenzoic acid, acac = acetylacetonate, TBHP = *tert*-butylhydroperoxide, L-Selectride = lithium tri-*sec*-butylborohydrate.

exclusively the undesired C3 α-stereoisomer (79% from **15a**) instead of **18**. Even under the hydroxy-directed dihydroxylation conditions of Donohoe,[18] the same undesired isomer was formed (76%). On the other hand, epoxidation of the enol ether **17** by using *m*-CPBA or the $VO(acac)_2$/TBHP system[19] did occur on the desired β-face of the molecule to produce the α-hydroxy ketone **18** with the desired C3 stereochemistry, but in a disappointingly low yield (<5%). To overcome the problem of low yield, the domino epoxidation–methanolysis protocol was employed.[20] Epoxidation with *m*-CPBA in MeOH in the presence of $NaHCO_3$ provided mixed ketal **19** as a single diastereoisomer in 82% yield (2 steps) from **15a**. Since α-hydroxy ketals are prone to rearrange under acidic conditions,[21] the deketalization of **19** was effected gently by catalytic hydrogenation of the benzyl group to give ketone **18**. Dihydroxyketone **18** itself was also found to be unstable[22] and readily decomposed to unidentified polar material. Thus, the best approach was to treat crude ketone **18** directly with the sterically demanding L-Selectride to give triol **20** as the sole stereoisomer in 92% overall yield from **19**.[23] Triol **20** was then protected to give triacetate **21** (92%).

B-Ring construction under Banwell's modified Bischler–Napieralski reaction conditions: After completing the functionalization of the C ring, we turned our attention to the construction of the B ring to complete the total synthesis. Banwell's modified Bischler–Napieralski reaction,[24] which is thought to proceed via an imino triflate intermediate, has been used widely for closure of the B ring in the synthesis of *Amaryllidaceae* alkaloids, including *trans*-dihydronarciclasine (**1**) and pancratistatin (**2**). However, literature examples of this reaction show it only to be effective for primary alkyl carbamate substrates.[2c–e] Thus, we were uncertain at that time that the Banwell procedure would be applicable to B-ring formation by using the *N*-Boc group in our case.

Under the standard Banwell reaction conditions (Tf_2O/DMAP = 5:3 molar ratio, 0 °C), we were able to obtain the desired cyclization product **22**, along with a minor amount of the regioisomer **23** from the *N*-Boc carbamate **21**, but in a very low yield (38%, Scheme 4). Interestingly, although the chemical yield was much lower (38 vs. 82%), the degree of regioselectivity in the B-ring formation was considerably higher than in the reported case, in which Banwell's modified Bischler–Napieralski reaction conditions were applied to the corresponding methoxycarbonyl compound **24** (11.5:1 vs. up to 3.6:1).[4a,b] This remarkable regioselectivity difference between the cyclization of substrates **21** and **24** under the same reaction conditions implied that the two cycloaddition reactions might proceed via different intermediates.

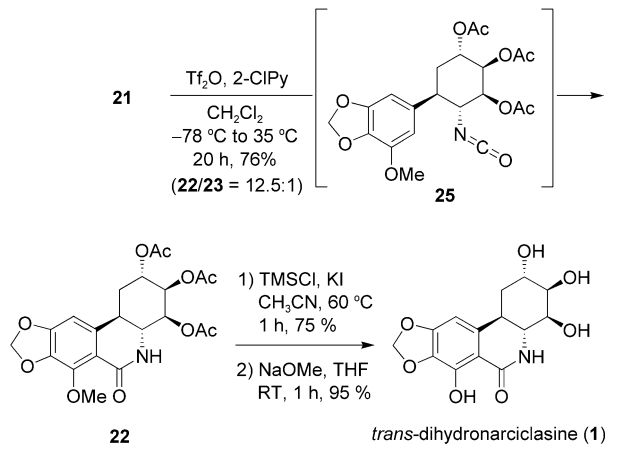
Recently, Schofield and co-workers observed that upon treatment with 2.0 equivalents of Tf_2O and 2.2 equivalents of Et_3N or pyridine, *N*-Boc-protected phenylalanine ester underwent dimerization to form a urea, most probably via an isocyanate intermediate.[25] This observation suggested the possibility that under Banwell's acidic reaction conditions, the *N*-Boc carbamate of **21** was converted to an isocy-



Scheme 4. B-ring construction under Banwell's reaction conditions. Tf_2O = trifluoromethanesulfonic anhydride.

anate through loss of its acid-labile *tert*-butyl group and dehydration, and this in situ generated isocyanate underwent intramolecular Friedel–Crafts-type cyclization.[26] After careful monitoring the reaction of **21** under the Banwell conditions, we could identify an unstable intermediate that was gradually converted to the cyclized products **22** and **23**. The identity of this intermediate was revealed to be isocyanate **25** (Scheme 5), primarily by IR spectroscopy (2253 cm^{-1}).

With these considerations in mind, efforts were made to find optimal reaction conditions for an intramolecular Friedel–Crafts-type cyclization of the *N*-Boc carbamate via an isocyanate intermediate. By varying the reaction conditions, we found that the desired conversion was greatly influenced by the amount of base present and the acidity of the reaction medium. We finally determined the optimal reaction conditions to be 1.1 equivalents of Tf_2O, 1.5 equivalents of 2-chloropyridine, and heating at 35 °C for 20 h. Under these conditions, the product **22** was obtained with very high regioselectivity (12.5:1) in 76% yield.



Scheme 5. Completion of the total synthesis. Py = pyridine.

The total synthesis was completed by demethylation with TMSCl/KI (75%) and removal of the acetate protecting groups with NaOMe (95%) to give (+)-**1**. The spectroscopic and optical-rotation data of the synthetic material were in good agreement with those reported for the natural product.

Conclusions

In conclusion, the total synthesis of (+)-*trans*-dihydronarciclasine (**1**) has been accomplished in 16% overall yield in a completely substrate-controlled manner from the readily accessible chiral starting material **9**. One of the unique features of this synthesis is the highly stereocontrolled introduction of the five contiguous stereogenic centers based on a single stereocenter in the starting material. Two of the five stereocenters were defined by an Ireland–Claisen rearrangement and the other three centers were created through diastereoselective reduction and oxidation reactions. The stereoselectivity for introducing all of the stereogenic reactions was excellent, with only a single diastereomer of each product being observed. The concise nature of this total synthesis hinges in part on the first demonstration of the successful conversion of a Claisen rearrangement product into a six-membered cyclic vinylogous ester by a regioselective Wacker-oxidation- and Dieckmann-condensation-based sequence. The successful B-ring formation with high regioselectivity from an *N*-Boc substrate via an isocyanate intermediate is also worth noting, and the present transformation is a useful complement to Banwell's variant of the Bischler–Napieralski reaction in the synthesis of dihydroisocarbostyrils from β-arylethylcarbamates.

Experimental Section

General methods and additional experimental details are given in the Supporting Information.

(2*R*,3*R*,*E*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*]-[1,3]dioxol-5-yl)hex-4-enoate (12): TBSCl (5.96 g, 39.54 mmol, 3.0 equiv) in THF (8 mL) was added to a stirred solution of ester **8** (5.00 g, 13.18 mmol, 1.0 equiv) in THF (80 mL). After the mixture was cooled to −78 °C, LHMDS (1.0 M solution in THF, 40 mL, 39.54 mmol, 3.0 equiv) was slowly added to the reaction flask over 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated NH_4Cl solution at 0 °C, stirred for another 1 h at room temperature, and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the desired acid **12-acid** as a single isomer, which was used in the next step without further purification. A small amount of pure acid was isolated by column chromatography on silica gel (hexane/EtOAc 2:1 + 1% AcOH) for ^1H NMR and HRMS analysis. ^1H NMR (400 MHz, CD_3OD): $\delta = 1.33$ (s, 9H), 1.65 (d, $J = 5.9$ Hz, 3H), 3.52 (t, $J = 8.6$ Hz, 1H), 3.85 (s, 3H), 4.34 (d, $J = 8.8$ Hz, 1H), 5.50–5.58 (m, 1H), 5.60–5.67 (m, 1H), 5.86 (d, $J = 3.4$ Hz, 2H), 6.42 (s, 1H), 6.44 ppm (s, 1H); MS (FAB): m/z: 402 $[M+23]^+$; HRMS (FAB): m/z calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1655.

The crude mixture obtained above was dissolved in MeOH (44 mL), and a solution of trimethylsilyl-diazomethane (2.0 M solution in diethyl ether, 17 mL, 32.95 mmol, 2.5 equiv) was added dropwise, causing instantaneous

bubbling, along with a change from colorless to yellow. After allowing the reaction to proceed for 1 h, the reaction was quenched with a small amount of acetic acid, at which time gas evolved and the reaction mixture became colorless. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc 4:1) to give the desired ester **12** (4.82 g, 93% for 2 steps) as a pale yellow solid. $[\alpha]_D^{25}$ −45.2 (c = 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9H), 1.67 (d, J = 5.1 Hz, 3H), 3.54–3.50 (m, 1H), 3.66 (s, 3H), 3.87 (s, 3H), 4.50 (t, J = 7.3 Hz, 1H), 4.78 (d, J = 7.6 Hz, 1H), 5.54–5.63 (m, 2H), 5.92 (s, 2H), 6.31 (s, 1H), 6.36 ppm (d, J = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.81, 28.02 (3C), 51.16, 51.71, 56.44, 57.76, 79.77, 101.23, 101.80, 107.36, 128.24, 128.87, 133.95, 134.10, 143.38, 148.88, 155.07, 172.02 ppm; IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3377, 2976, 1744, 1715, 1634, 1510, 1452 cm^{-1}; MS (FAB): m/z: 394 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{20}H_{28}NO_7$: 394.1866 $[M+H]^+$; found: 394.1972.

The diastereomeric purity of ester **12** was determined by crude ^{1}H NMR spectrum analysis. The enantiomeric purity of ester **12** (>99% *ee*) was determined by chiral HPLC analysis (CHIRALCEL OJ-H, 2-propanol/hexane (0 to 10%, 60 min), flow rate: 0.5 mL min^{-1}, t_R (chiral sample) = 37.7 min [(−)-isomer]; t_R (racemic sample) = 37.1 [(−)-isomer], 42.5 min [(+)-isomer], detected at 225 nm).

(2*R*,3*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*]-[1,3]dioxol-5-yl)-5-oxohexanoate (13): $HClO_4$ (1.0 M solution in CH_3CN, 2.0 mL, 2.03 mmol, 0.2 equiv) was added to a mixture of $Pd(OAc)_2$ (685 mg, 3.05 mmol, 0.3 equiv) and 1,4-benzoquinone (1.10 g, 10.17 mmol, 1.0 equiv) in CH_3CN/H_2O (7:1, *v*/*v*, 51 mL). The resulting solution was stirred 1 h at room temperature and ester **12** (4.00 g, 10.17 mmol, 1.0 equiv) was added to the reaction flask. After being stirred for 6 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution at 0°C, and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Owing to similar R_f values for the hydroquinone generated and the product under various eluent conditions, hydroquinone was acetylated under standard conditions (Ac_2O, Et_3N, DMAP, CH_2Cl_2). The resulting crude mixture was purified by flash column chromatography on silica gel (hexane/EtOAc 2:1) to give the desired methyl ketone **13** (3.41 g, 82%) as a pale brown oil. $[\alpha]_D^{25}$ −55.3 (c = 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 2.13 (s, 3H), 2.67 (dd, J = 5.4, 17.7 Hz, 1H), 2.98 (dd, J = 8.4, 17.8 Hz, 1H), 3.70 (s, 3H), 3.78 (brs, 1H), 3.86 (s, 3H), 4.60 (d, J = 5.0 Hz, 1H), 4.97 (d, J = 8.3 Hz, 1H), 5.92 (s, 2H), 6.26 (d, J = 1.3 Hz, 1H), 6.31 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.14 (3C), 30.14, 42.25, 45.14, 52.10, 56.47, 56.58, 79.96, 101.31, 101.64, 108.10, 133.00, 134.46, 143.30, 148.94, 155.70, 171.40, 205.80 ppm; IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3381, 2978, 1714, 1633, 1510, 1452, 1435 cm^{-1}; MS (FAB): m/z: 409 $[M]^+$; HRMS (FAB): m/z calcd for $C_{20}H_{27}NO_8$: 409.1737 $[M]^+$; found: 409.1749.

***tert*-Butyl (1*R*,2*R*,6*R*)-4-(benzyloxy)-2-hydroxy-6-(7-methoxybenzo[*d*]-[1,3]dioxol-5-yl)cyclohex-3-enylcarbamate (17)**: Red-Al (sodium bis(2-methoxyethoxy)aluminum dihydride, 70% in toluene, ca. 3.6 M, 1.8 mL, 6.42 mmol, 1.5 equiv) was slowly added to a stirred solution of vinylogous benzyl ester **15a** (2.00 g, 4.28 mmol, 1.0 equiv) in THF (43 mL) at 0°C. The reaction mixture was stirred for 30 min at 0°C and then quenched by the addition of saturated NH_4Cl solution at 0°C and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give allylic alcohol **17** as a single isomer. Owing to its instability under acidic conditions, the resulting pale yellow oil was used in the next step without further purification. The diastereomeric purity of alcohol **17** was determined by crude ^{1}H NMR spectrum analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.40 (dd, J = 5.1, 16.8 Hz, 1H), 2.52 (t, J = 16.8 Hz, 1H), 2.89 (dt, J = 5.5, 11.5 Hz, 1H), 3.69 (td, J = 7.1, 11.8 Hz, 1H), 3.89 (s, 3H), 4.41 (brs, 2H), 4.67–4.90 (m, 3H), 5.90–6.00 (m, 2H), 6.38–6.44 (m, 2H), 7.27–7.42 ppm (m, 5H).

***tert*-Butyl (1*R*,2*S*,3*S*,4*R*,6*R*)-4-(benzyloxy)-2,3-dihydroxy-4-methoxy-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohexylcarbamate (19)**: $NaHCO_3$ (1.08 g, 12.84 mmol, 3.0 equiv) and *m*-CPBA (1.11 g, 6.42 mmol, 1.5 equiv) were added at 0°C to the crude mixture of allylic alcohol **17** obtained in the previous step in MeOH (22 mL). The reaction mixture was stirred for 2 h at room temperature and then quenched by the addition of saturated $Na_2S_2O_3$ solution at 0°C and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:2) to give ketal **19** (1.82 g, 82% for 2 steps from **15a**) as a single isomer. $[\alpha]_D^{25}$ +11.8 (c = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 1.29 (s, 9H), 2.02 (dd, J = 2.0, 13.9 Hz, 1H), 2.12 (t, J = 13.9 Hz, 1H), 2.51 (dt, J = 3.5, 12.5 Hz, 1H), 3.27 (s, 3H), 3.73 (dd, J = 2.5, 9.8 Hz, 1H), 3.86 (s, 3H), 3.91 (brs, 1H), 4.13 (s, 1H), 4.38 (d, J = 7.9 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 5.90 (d, J = 3.2 Hz, 2H), 6.40 (d, J = 3.8 Hz, 2H), 7.26–7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.07 (3C), 34.95, 43.21, 47.81, 54.94, 56.46, 62.33, 70.87, 73.64, 79.77, 100.99, 101.19, 101.97, 106.77, 127.33, 127.42 (2C), 128.26 (2C), 133.89, 135.89, 138.08, 143.49, 148.71, 157.19 ppm; IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3398, 2973, 1691, 1635, 1515 cm^{-1}; MS (FAB): m/z: 518 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{27}H_{36}NO_9$: 518.2390 $[M+H]^+$; found: 518.2377.

(2*S*,3*R*,4*S*,4a*R*,11b*R*)-7-Methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-2,3,4-triyl triacetate (22): 2-Chloropyridine (1.0 M solution in CH_2Cl_2, 0.3 mL, 0.29 mmol, 1.5 equiv) and triflic anhydride (0.2 M solution in CH_2Cl_2, 1.1. mL, 0.21 mmol, 1.1 equiv) were added to a stirred solution of triacetate **21** (100 mg, 0.19 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) at −78°C. After stirring at −78°C for 30 min, the reaction mixture was warmed to 35°C and stirred for an additional 20 h. After that, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0°C. This was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/acetone 1:1) to give the major isomer **22** (65 mg, 76%) as a white solid, along with the minor isomer **23** (5 mg, 6%). $[\alpha]_D^{25}$ +131.3 (c = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64 (brs, 1H), 1.85 (dt, J = 2.8, 13.6 Hz, 1H), 2.05 (s, 6H), 2.12 (s, 3H), 2.38 (d, J = 14.4 Hz, 1H), 3.05 (dt, J = 3.8, 12.4 Hz, 1H), 3.64 (t, J = 11.6 Hz, 1H), 4.04 (s, 3H), 5.13 (d, J = 3.0 Hz, 1H), 5,16 (d, J = 3.0 Hz, 1H), 5.40 (t, J = 3.0 Hz, 1H), 5.98 (d, J = 7.8 Hz, 2H), 6.14 (brs, 1H), 6.44 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.68, 20.76, 21.02, 26.95, 35.94, 52.12, 60.81, 67.37, 68.57, 71.49, 98.98, 101.68, 115.51, 137.13, 137.41, 145.08, 152.06, 163.75, 169.13, 169.38, 170.37 ppm; IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3197, 2926, 1752, 1669, 1612 cm^{-1}; MS (FAB): m/z: 450 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{21}H_{24}NO_{10}$: 450.1400 $[M+H]^+$; found: 450.1409.

(+)-*trans*-Dihydronarciclasine (1): KI (18.4 mg, 0.11 mmol, 1.0 equiv) and TMSCl (0.5 M solution in CH_3CN, 0.3 mL, 0.14 mmol, 1.3 equiv) were added to a stirred solution of lactam **22** (50.0 mg, 0.11 mmol, 1.0 equiv) in CH_3CN (5 mL). The reaction mixture was stirred for 1 h at 60°C and quenched by the addition of H_2O at 0°C. This was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to give **22-OH** (36.2 mg, 75%) as a white solid. $[\alpha]_D^{25}$ +81.8 (c = 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (dt, J = 2.7, 13.5 Hz, 1H), 2.07 (s, 6H), 2.12 (s, 3H), 2.41 (d, J = 14.5 Hz, 1H), 3.12 (dt, J = 3.6, 12.6 Hz, 1H), 3.76 (dd, J = 11.0, 12.7 Hz, 1H), 5.14–5.20 (m, 2H), 5.42 (t, J = 3.0 Hz, 1H), 5.98 (brs, 1H), 6.02 (d, J = 4.1 Hz, 2H), 6.31 (s, 1H), 12.29 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.70, 20.78, 21.03, 26.67, 34.55, 52.75, 67.23, 68.43, 71.62, 96.71, 102.33, 106.94, 133.18, 135.78, 146.47, 152.95, 169.15, 169.33, 170.13 ppm (2C); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3335, 2924, 1752, 1673, 1627 cm^{-1}; MS (FAB): m/z: 436 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{20}H_{22}NO_{10}$: 436.1244 $[M+H]^+$; found: 436.1245.

NaOMe (1.0 M solution in MeOH, 0.7 mL, 10.0 equiv) was added to a solution of **22-OH** (30.0 mg, 0.07 mmol, 1.0 equiv) in THF (7 mL). After being stirred at room temperature for 1 h, the reaction was quenched by the addition of saturated NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH 10:1) to give (+)-*trans*-dihydronarciclasine **1** (20.3 mg, 95%) as a white solid. $[\alpha]_D^{25}$ +4.0 (c = 0.16, THF), (literature[4b] $[\alpha]_D^{25}$ +4.1 (c = 0.22, THF)); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.78–1.87 (m, 1H), 2.17–2.25 (m, 1H), 2.99 (dt, J = 3.4, 12.6 Hz, 1H), 3.46

(dd, $J=10.1$, 13.0 Hz, 1H), 3.85 (dd, $J=3.0$, 10.1 Hz, 1H), 3.90 (t, $J=2.9$ Hz, 1H), 4.04–4.09 (m, 1H), 5.99 (d, $J=2.4$ Hz, 2H), 6.44 ppm (s, 1H); ^{13}C NMR (125 MHz, CD_3OD): $\delta=0.43$, 36.06, 57.17, 71.35, 72.33, 74.14, 98.47, 104.22, 109.05, 134.72, 140.53, 148.06, 155.10, 172.70 ppm; IR (neat): $\tilde{\nu}_{max}=3354$, 2923, 1625 cm^{-1}; MS (FAB): m/z: 310 $[M+1]^+$; HRMS (FAB): m/z calcd for $C_{14}H_{16}NO_7$: 310.0927 $[M+H]^+$; found: 310.0928.

Acknowledgements

This work was supported by the SRC/ERC program (R-11-2007-107-02001-0) and the WCU program (R32-2008-000-10098-0) of the National Research Foundation of Korea (NRF) grant founded by Korea government (MEST).

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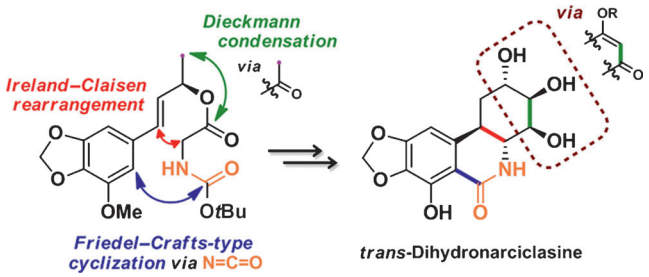
Received: May 10, 2012
Published online: ■■ ■■, 0000



A highly selective and efficient total synthesis of (+)-*trans*-dihydronarciclasine was developed. The synthesis defines two of the five stereocenters in an amino acid ester–enolate Claisen rearrangement. The other three stereocenters are created via a cyclic vinylogous ester intermediate, which was generated from the γ,δ-unsaturated ester functional group of the rearrangement product. The B ring is constructed by a Friedel–Crafts-type cyclization, exemplifying the use of an *N*-Boc group to generate an isocyanate intermediate (see scheme).

Natural Product Synthesis

*S. Hwang, D. Kim, S. Kim** ▮▮▮▮–▮▮▮▮

Stereocontrolled Total Synthesis of (+)-*trans*-Dihydronarciclasine